Pathophysiological and clinical studies on Crohn’s disease in children

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ABSTRACT

Crohn’s disease (CD) is often diagnosed in late childhood and early adulthood. Clinical findings include abdominal pain, diarrhea, rectal bleeding, perianal lesions, weight loss and growth retardation. Extra-intestinal manifestations, strictures and fistulas may complicate the disease. The disease course is characterized by a chronic relapsing pattern and disease severity varies between individuals. Environmental, genetic and immunological factors influence the development of CD. The exact mechanisms are not clear, but there are probably individual combinations of aberrations that contribute to the heterogeneity of the disease phenotype. NOD2/CARD15 gene polymorphisms are reported in up to 60% of CD patients and are associated with ileal disease, more complicated disease behaviour and younger age at onset. The diagnosis of CD is based on clinical, endoscopic and radiological findings. Presence of epithelioid cell granulomas in intestinal biopsies is one, non-compulsory, criterion of CD, but the reason why some patients have granulomas and not others is elusive. The treatment regimen of pediatric CD is moving towards an early, more aggressive approach, aiming at preventing disease progression and complications, such as growth retardation. However, reliable prognostic markers are lacking and it is difficult to predict which patient would benefit most from aggressive treatment.

The aim of this thesis is to broaden the knowledge of genetic, histopathological and clinical factors that may be related to the disease course of CD in children.

In paper I the prevalence of and influence from the main NOD2/CARD15 polymorphisms in Swedish pediatric CD patients is described. NOD2/CARD15 polymorphisms are uncommon; a single allele variant is present in only 8.6% of the patients and genotype-phenotype correlations are difficult to establish.

In paper II the correlation between the location of the disease and the age at onset of CD in children is investigated. Ileal involvement before the age of nine is rare and the probability of ileal disease increases with age until adulthood. Isolated ileitis is seldom found in pediatric CD and, consequently, ileal involvement is most often associated with colonic disease.

In paper III the effects of interleukin (IL)-6 and variants of the IL6 gene on growth is studied in an animal colitis model and in pediatric CD patients. In rats with induced colitis, IL-6 causes growth suppression. Blocking IL-6 with antibodies results in increased IGF-I levels and enhanced growth, but without improvement of the intestinal inflammation or increased food intake among the rats. The children studied with the IL6 -174 GG genotype, which previously has been associated with higher IL-6 levels, are more growth-retarded at diagnosis compared to other genotypes. This indicates a negative influence on growth as a consequence of a higher expression of IL-6.

In paper IV the significance of granuloma findings in biopsies in pediatric CD patients is evaluated. A description of clinical characteristics and growth of a pediatric CD cohort followed into adulthood is also performed. Granulomas are found in half of the patients at onset and are associated with both upper gastrointestinal involvement and a shorter time to initiating immune modulating agents (i.e. thiopurines, methotrexate or anti-TNF-α), suggesting an association with a more aggressive disease. The follow-up (median 12.3 years) shows that this Swedish group of childhood onset CD has more colonic disease and less ileal involvement, and that growth impairment is infrequent both at onset and at follow-up.

This thesis adds to the growing knowledge of the etiological and prognostic factors in CD in children. Due to the complex pathophysiology of CD and the heterogeneity of the phenotype, large-scale, multicenter trials, in which genetic, clinical, serologic and environmental information is combined, would be valuable to accurately determine the risks and prognosis for each afflicted individual. The ultimate goal is to develop personalized therapy strategies, with the aim of improving prognosis and quality of life of patients with this disease.

Keywords: age, colitis, Crohn’s disease, granuloma, growth, ileitis, inflammatory bowel disease, interleukin 6, NOD2/CARD15, pediatrics, prognosis